Claim 18 has been amended to recite a method for the treatment of acute pain. Thus, it is believed that claim 18 is definite to one of ordinary skill in the art and satisfies the requirements of 35 USC 101.

Claims 1-20 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-21 of co-pending application No. 09/787,888. This rejection is traversed.

Enclosed with this amendment is a terminal disclaimer directed to application No. 09/787,888. Thus, it is believed to be apparent that the double patenting rejection has been obviated.

Claims 1-20 were rejected under 35 USC 103(a) as allegedly being unpatentable over NYSTROM in view of knowledge in the art. This rejection is respectfully traversed.

Applicants respectfully submit that the Official Action uses an impermissible approach in determining whether the claimed invention is obvious in view of NYSTROM and the knowledge in the art.

In imposing the rejection, the outstanding Official Action dissects the claims into allegedly essential elements and non-essential elements. Applicants traverse this dissection of the claims in this manner. Moreover, it is entirely unclear how the Examiner has even categorized certain portions of the claims as essential and other portions as non-essential.

Applicants note that 35 USC 103(a) provides that the "subject matter as a whole" must be considered. Moreover, applicants note that *Graham v. John Deere Co.*, 383 US 1, 148 USPQ 459 (1966) establishes the following considerations for determining obviousness under 35 USC 103(a):

(1) determining the scope and contents of the prior art;

(2) ascertaining the differences between the prior art and the claims at issue;

(3) resolving the level of ordinary skill in the pertinent art; and

(4) considering objective evidence present in the application indicating obviousness or non-obviousness.

Thus, it is clear that the relevant case law and statute fails to make any reference to dissecting a claim on the basis of its essential and non-essential elements.

It is respectfully submitted that the outstanding Official Action fails to utilize the appropriate approach for determining obviousness under 35 USC 103(a).

Applicants respectfully submit that the teachings of NYSTROM in view of the knowledge in the art available to one of ordinary skill in the art at the time the application was filed, would not lead one of ordinary skill in the art to the claimed invention. Applicants believe that it would not have been obvious to one of ordinary skill in the art to utilize ordered

interactive mixtures in combination with mucoadhesive promoting agents as set forth in the present application. As noted in the present specification on page 4, applicants have unexpectedly discovered that an ordered mixture may be utilized in a sublingual administration of an active ingredient. Particularly, ordered mixtures require a relative large volume of liquid in order to be effective. However, in the sublingual administration of an ordered mixture, the volume of liquid available as a solvent is limited to a few millimeters.

On page 6, the Official Action contends, "NYSTROM clearly names the bio/mucoadhesive (microcrystalline cellulose)..." and that NYSTROM provides the general combination of active agent particles with bio/mucoadhesive particles, along with suggestions for specific excipients. However, applicants respectfully traverse this assertion.

Applicants note that NYSTROM fails to mention muco- or bioadhesive components. In this respect, NYSTROM fails to disclose or suggest a combination of ordered mixtures and mucoadhesive agents. Moreover, applicants note that one of ordinary skill in the art would appreciate that microcrystalline cellulose does not have bio/mucoadhesive properties. In fact, applicants have amended the claims and specification to correct this obvious error. Thus, applicants respectfully submit that NYSTROM fails to disclose or suggest the claimed invention.

It is true that mucoadhesion promoting agents have been used to significantly increase the time period for drug release at a specific absorption site. For example, buccal tablets and gel formulations have been utilized to obtain the extended release of drugs into the body.

However, for these types of systems, it is the entire dosage form that possesses the mucoadhesive properties. In the present invention, the dosage form does not have to remain intact (slowly releasing its content of drug), but it can quickly disintegrate to a large number of mucoadhesive subunits, which can attach to the sublingual mucosa for a relatively short period of time.

Thus, the mucoadhesive promoting agent in the present invention is not just "added to the composition" resulting in general mucoadhesive properties of the entire coherent dosage form, but rather, the mucoadhesion promoting agent may be added in a particulate form. Moreover, the agent may be specifically added to the "ordered units". They may be added to a peripheral position onto the carrier particles in the ordered units. Then, the carrier particles can then be retained in the sublingual position.

Thus, applicants respectfully submit that the Official Action fails to meet its burden in rendering the claimed invention obvious. It is respectfully submitted that the cited

publications in the outstanding Official Action fail to disclose or suggest the following:

(a) the physical state of such a mucoadhesive agent;

(b) the way of admixing the agent; and

(c) the position of the agent within the composition.

Applicants also respectfully submit that the outstanding Official Action fails to disclose or suggest the use of the combination of ordered mixtures in combination with the sublingual administration.

Ordered mixtures have been used to obtain a rapid dissolution of an active ingredient. This is based upon the prerequisite that the carrier is instantly dissolved thus rapidly liberating individual, discrete drug particles which subsequently are rapidly dissolved. One of ordinary skill in the art would expect that a relatively large volume of solvent is required. However, when a preparation is administered sublingually, a large volume of solvent is not present.

While applicants note the Official Action rejects the claims over NYSTROM in view of the "knowledge in the art", applicants believe that the FINE et al. and STANLEY publications fail to remedy the deficiencies of NYSTROM. None of the publications cited in the Official Action disclose or suggest the claimed pharmaceutical composition or the claimed method.

While the Official Action attempts to show that individual components of the claimed invention are known, it is

believed that the Official Action fails to consider the subject matter of the claimed invention as a whole. As a result, applicants believe the proposed rejection fails to establish the motivation and reasonable expectation of success necessary to establish a *prima facie* case of obviousness.

With regard to claims 2, 3, 7, 11, 17 and 20, the Official Action contends that the specific concentrations and dosages for the composition are non-critical and obviated by the prior art. In support of this contention, the Examiner cites *In re Aller* and *In re Russell*. However, applicants traverse this contention.

As the Examiner is aware, a particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation or what may be well known in the art. *In re Antoine*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). None of the cited publications in the outstanding Official Action disclose or suggest that the ranges and dosages set forth in the claimed invention may act as result-effective variables. Thus, it is respectfully submitted that it would not be obvious to one of ordinary skill in the art to optimize the claimed ranges and dosages.

Attached hereto is a marked-up version of the changes made to the specification and claims. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph beginning at page 6, line 14, has been amended as follows:

A variety of polymers known in the art can be used as bio/mucoadhesion promoting agents. In addition to their polymeric nature, their ability to swell is important. On the other hand, it is also important that they are substantially insoluble in water. Their swelling factor by volume when brought into contact with water or saliva should preferably be at least 10, while a factor of at least 20 is more preferred. Examples of such bio/mucoadhesion promoting agents include cellulose derivatives such as hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose and sodium carboxymethyl cellulose (NaCMC); starch derivatives such as moderately cross-linked starch; acrylic polymers such as carbomer and its derivatives (Polycarbophyl, Carbopol®, etc.); polyethylene oxide (PEO); chitosan (poly-(D-glucosamine)); natural polymers such as gelatin, sodium alginate, pectin; scleroglucan; xanthan gum; guar gum; poly co-(methylvinyl ether/maleic anhydride); [microcrystalline cellulose (Avicel®);] and crosscaramellose. Combinations of two or more bio/mucoadhesive polymers can also be used. More generally, any physiologically acceptable agent showing bio/mucoadhesive

characteristics may be used successfully to be incorporated in the carrier.

IN THE CLAIMS:

Claim 3 has been amended as follows:

3. (twice amended) A composition according to claim 1, comprising from 0.05 to 5 weight percent of fentanyl[, preferably then from 0.1 to 1 weight percent].

Claim 5 has been amended as follows:

5. (twice amended) A composition according to claim 1, wherein the mean sieve diameter of the carrier particles is less than 750 µm[, preferably then from 100 to 600 µm].

Claim 7 has been amended as follows:

7. (amended) A composition according to claim 1, wherein the carrier particles contain from 0.1 to 25 weight percent of the bio/mucoadhesion promoting agent[, preferably then from 1 to 15 weight percent,] based on the total composition.

Claim 9 has been amended as follows:

9. (amended) A composition according to claim 8, wherein the bio/mucoadhesion promoting agent is selected from the group consisting of cellulose derivatives and comprising hydroxypropylmethyl cellulose, hydroxyethyl cellulose,

hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, [microcrystalline cellulose] and modified cellulose gum; crosscaramellose; modified starch; acrylic polymers comprising carbomer and its derivatives; polyethylene oxide; chitosan; gelatin; sodium alginate; pectin; scleroglucan; xanthan gum; guar gum; poly-co-(methyl vinyl ether-maleic anhydride); and mixtures thereof.

Claim 11 has been amended as follows:

11. (amended) A composition according to claim 10, wherein the surfactant is present in an amount from 0.5 to 5 weight percent of the composition[, preferably then 0.5 to 3 weight percent].

Claim 18 has been amended as follows:

18. (amended) [The use of] A method for the treatment of acute pain, comprising administering to an individual in need thereof, an effective amount of fentanyl or a pharmaceutically acceptable salt thereof in microparticle form for the preparation of an essentially water-free pharmaceutical composition for the treatment of acute pain [by sublingual administration], wherein [the] microparticles are adhered to [the] surfaces of carrier particles which are substantially larger than said microparticles and are essentially water-soluble, and a bioiadhesion and/or

mucoadhesion promoting agent is mainly adhered to the surfaces of said carrier particles.